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10/581,911	06/07/2006	Naoko Kida	Q95279	8940

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SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
UNDERDAHL, THANE E	
ART UNIT	**PAPER NUMBER**
1651	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/581,911	KIDA ET AL.	
	Examiner	Art Unit	
	Thane Underdahl	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 8/1/07.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the Applicant's reply received 8/1/07. Claims 1-9 are pending. No claims are withdrawn. No claims are cancelled. Claims 1 and 6 have been amended. No claims are new.

Response to Applicant's Arguments— 35 U.S.C § 112

In the response submitted by the 35 U.S.C § 112 rejection of claim 6 is withdrawn in light of the Applicant's amendment.

Response to Applicant's Arguments— 35 U.S.C § 102

In the response submitted by the Applicant, the 35 U.S.C § 102 (b) rejection of claims 1-5 and 9 over Goodwin et al., Schwarz et al. a with support from Unsworth et al. were considered but not found persuasive.

The Applicant argues that the claimed method is not expressly or inherently disclosed in Goodwin et al. because "the claimed method involves the use of cells other than cartilage cells' to produce cartilage tissue" such as the production of cartilage tissue using bone marrow cells. (Applicant's Response page 7). However the Examiner will point out that method claims are definded by their steps. The only active step in claim 1 is the culturing bone marrow mesenchymal stem cells in a simulated microgravity environment. While the preamble of claim 1 states "A method for engineering cartilage tissue". M.P.E.P. § 2111.02 state:

> "The determination of whether preamble recitations are structural limitations or mere statements of purpose or use "can be resolved only on review of the entirety of the [record] to gain an understanding of what the inventors actually invented and intended to encompass by the claim".

And further states:

> "a preamble generally is not limiting when the claim body describes a structurally complete invention such that deletion of the preamble phrase does not affect the structure or steps of the claimed invention." Consequently, "preamble language merely extolling benefits or features of the claimed invention does not limit the claim scope without clear reliance on those benefits or features as patentably significant."

In short the active step in claim 1 of "culturing bone marrow mesenchymal cells in a simulated microgravity environment" is a method that stands alone. The preamble of using the this step to engineer cartilage tissues is simply an intended use. Futhermore the claim simple states that the step is for engineering cartilage tissue not that cartilage tissue is made. In the broadest interpretation of the claim the cartilage tissues need not be made by the bone marrow cells but could be a component of the engineered cartilage tissues such as a sandwich layer of cartilage tissue and mesenchymal cells from bone marrow. Simple put, Goodwin et al. describes the active step of culturing the bone marrow cells in a simulated microgravity environment, and thus meets the limitations of claim 1, regaurdeless what the use of the cultured cells. Furthermore Goodwin et al. still meets the amended limitation of "bone marrow mesenchymal cells" since bone marrow is a mixture of cells which inherently includes mesenchymal cells.

The Applicant argues that the size of the tissue disclosed by Goodwin et al. teaches the production of a "spheroid" rather than a tissue. This argument is not commensurate with the scope of the claims since there is no limitation expressed in the

claims defining the size and extent of the tissue. Furthermore, the Applicant argues that the product of Goodwin should be called a "spheroid" rather than a "tissue". This argument is merely the argument of counsel and is unsupported by evidence or declarations of those skilled in the art. Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See M.P.E.P. § 2129 and § 2144.03 for a discussion of admissions as prior art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964); and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). See M.P.E.P. § 716.01(c) for examples of attorney statements that are not evidence and that must be supported by an appropriate affidavit or declaration.

The Applicant argues that the RWV vessel used by Goodwin et al. differers from the claimed invention since "the present invention balances the tissues in the RWV vessel in order to maintain their relative positions"(Applicant Response, page 8). This argument is not commensurate with the scope of the claims since there is no limitation expressed in the claims defining a "balancing" of the rotational speed, only that in claim 6 that the rotational speed be a range of 8.5 to 25 rpm.

The Applicant argues the type of collagen that is intended to be made with the method. Again, this argument is not commensurate with the scope of the claims since there is no limitation expressed in the active step of the claim 1 where any type of collagen is produced.

The Applicant argues that "The purpose of the present invention is three-dimensional tissue engineering by culturing bone marrow cells in a simulated microgravity environment to control the differentiate of the cells" (Applicant Response, page 9). However in claims 1-5 and 9 there is no step defining the differentiation of the cells only that cells were cultured in a microgravity environment. Therefore, this argument is not commensurate with the scope of the claims.

The Applicant argues that the system of the incorporated reference is to a bioreactor system where the cells are grown on microcarier beads. Nothing in the claim language states that microcarrier beads are excluded from the bioreactor. The Applicant argues continues to argue that Unsworth et al. is a general reference that does not apply to the teachings of Goodwin et al. or Schwarz et al. However Unsworth et al. teach the general performance characteristics of RVW's like those used by Goodwin et al. and Schwarz et al. and even cites papers by Goodwin (see reference 30 of Unsworth et al.).

Therefore the rejection stands and is repeated below with modifications to address the claim amendments.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5 and 9 remain rejected under 35 U.S.C. 102(b) as being anticipated by Goodwin et al. (U.S. Patent # 5,496,722, 1996) and Schwarz et al. (U.S. Patent #

5,026,650, 1991) with support from Unsworth et al. (Nature Medicine, 1998). The reason why two references are cited for this 35 U.S.C § 102(b) rejection is that Goodwin et al. expressly incorporates the patent of Schwartz et al. in their application (Goodwin et al., col 8, lines 5-10). M.P.E.P. § 2163.07(b) states:

> "Instead of repeating some information contained in another document, an application may attempt to incorporate the content of another document or part thereof by reference to the document in the text of the specification. The information incorporated is as much a part of the application as filed as if the text was repeated in the application, and should be treated as part of the text of the application as filed."

Therefore it is proper to include the information of the incorporated reference as if it were included in the parent document and as such treated as if it were the same document when applied against the current claims.

These claims are drawn to a method grow bone marrow cells into a three-dimensional (**3D**) tissue in a simulated microgravity environment. Claim 2 limits the gravity to 10^{-1} to 10^{-2} of ground gravity on a time average basis. This microgravity is achieved using a uniaxial rotary bioreactor such as a Rotating Wall Vessel (**RWV**). Claim 9 limits that the bone marrow cells are isolated from a subject in need of transplantation of the engineered cartilage tissue.

Goodwin et al. teach a method of culturing bone marrow cells (which inherently contain mesenchymal cells) in a 3D into a tissue in a simulated microgravity

environment (Goodwin et al. col 4, lines 36-45). This microgravity environment is simulated by a RWV (Goodwin col 8, lines 5-10) which compensates ground gravity with the stress of the rotating vessel (Schwarz, col 6, lines 5-15). RWVs simulate an environment of 10^{-2} of ground gravity as supported by Unsworth et al.(Unsworth et al., page 902, col 1). Goodwin et al. further teach that bone marrow can be obtained from the patient, tissue grown and then transplanted back to the patient (Goodwin col 5, lines 5-12). Therefore the reference anticipates claims 1-5 and 9.

Response to Applicant's Arguments— 35 U.S.C § 103

In the response submitted by the Applicant, the 35 U.S.C § 103 (a) rejection of claims 1-5, 8 and 9 over Goodwin et al. and Schwarz were considered but not found persuasive.

The Applicant continues to argue the aspect of the invention is to produce cartilage. However as stated above, methods are defind by their active steps and the active steps of of claim 1-5, 8 and 9 do not include a step for cartilage production on the culturing of bone marrow mesenchymal cells in a simulated microgravity environment. Therefore any further argument concerning the cartilage is not commensurate with the scope of the claims.

The Applicant argues that Goodwin et al. "only describes that cell proliferation derease with time in a two dimensional culture" and that they "do not teach or sugest that under a confluent condition matrix production becomes more active than cell proliferation" (Applicant Response, page 13). This argument is not commensurate with

the scope of the claims since no limitation discussing matrix production is included in the current set of claims.

The Applicant further argues that the conditions listed in claim 6 are not a matter of routine optimization and could not have been discovered by routine optimization. This argument is merely the argument of counsel and is unsupported by evidence or declarations of those skilled in the art. Attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See M.P.E.P. § 2129 and § 2144.03 for a discussion of admissions as prior art. Counsel's arguments cannot take the place of objective evidence. *In re Schulze*, 145 USPQ 716 (CCPA 1965); *In re Cole*, 140 USPQ 230 (CCPA 1964); and especially *In re Langer*, 183 USPQ 288 (CCPA 1974). See M.P.E.P. § 716.01(c) for examples of attorney statements that are not evidence and that must be supported by an appropriate affidavit or declaration. Furthermore the M.P.E.P. § 2131.03 state:

> Applicants can rebut a *prima facie* case of obviousness based on overlapping ranges by showing the criticality of the claimed range. "The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. . . . In such a situation, the applicant must show that the particular range is critical, generally by showing that the claimed range achieves unexpected results relative to the prior art range."

In short, one of ordinary skill in the art would recognize that cell concentration, rotation speed and the size of the vessel are result-effective variables and in the absence of

evidence to the contrary or to some unexpected result would meet the limitations of claim 6.

The Examiner is confused as to the argument about TGF-β in this rejection since that is a limitation of claim 7 which is not addressed in this rejection of claims 1-5, 8 and 9. Clarification is required.

Therefore the rejection stands and is repeated below.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 8 and 9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Goodwin et al. and Schwarz et al. as applied to claims 1-5 and 9.

The description and rejection of claims 1-5 and 9 are described in the 35 U.S.C § 102(b) rejection above. Claim 8 limits that the bone marrow cells of claim 1 must be two-dimensionally cultured to confluence, subculture and then cultured in a simulated microgravity environment.

Goodwin et al. teach their 3D bone marrow tissue is bone marrow cells (col 6, lines 35-45). Goodwin et al. also teach that bone marrow cells are cultured in a 2D culture (col 4, lines 20-25). Goodwin et al. also teach that "In the case of preparing bone marrow for recipients volumes are expanded as cellular densities or metabolic requirements dictate. The limited parameters may depend on the rotating vessel's ability to suspend large aggregates" (col 14, lines 25-34). One of ordinary skill in the art would recognize

that this is a form of sub-culturing cellular bone marrow cells before being added to the RWV and that the "aggregates" of bone marrow Goodwin is referring to are confluent tissues of bone marrow cells. Goodwin et al. also teaches that 2D bone marrow cell cultures have a decreased production over time (col 4, lines 20-25). It would have been obvious to someone skilled in the art to start the bone marrow culture from the primary cells then transfer it to a 2D culture flask to produce bone a marrow monolayer for aggregates that can be cultured in a RWV. One of ordinary skill in the art would recognize that culturing a monolayer of bone marrow is to confluence. The motivation is provided by Goodwin et al. who state that while it is possible to culture bone marrow monolayers in 2D the bone marrow cell production decreases over time (col 4, lines 20-25). Therefore if Goodwin et al. desires an expansion of the bone marrow cells, it would be obvious to culture the aggregates from a 2D monolayer in a microgravity environment where Goodwin et al. has shown reasonable expectation of success by achieving high cell densities in a 3D structure. Therefore, the invention as a whole would have been prima facie obvious at the time of filing in view of the references listed above and as such claims 1-5, 8 and 9 are not allowable.

In the response submitted by the Applicant, the 35 U.S.C § 103 (a) rejection of claims 1-6 and 9 over Goodwin et al. and Schwarz et al. in further view of Synthecon were considered but not found persuasive.

The Applicant argues that Synthecon does not teach a RWV. However, one of ordinary skill in the art would recognize that Synthecon makes batch Rotary Cell Culture

systems (see page 1) which one of ordinary skill in the art would recognize are synonomous with RWV. The citation of page 2 is to show that Synthecon can build custom RWV that adjusted the size (i.e. the diameter) of the vessel. This small reference taken as a whole cleary shows that the limitations of claim 6 such as the diameter of the vessel can be met through routine optimization by one of ordinary skill in the art (M.P.E.P. § 2144.05).

Furthermore the argument that the RollerCell 40 which the Applicant asserts is only used by those skilled in the art for culturing of monolayers. However the customization of the size of the RWV cited on page 2 refers only to the Rotary Cell Culture Systems and not the RollerCell 40.

Therefore the rejection stands and is repeated below.

Claims 1-6 and 9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Goodwin et al. and Schwarz et al. as applied to claims 1-5 and 9 above, and further in view of Synthecon (http:/synthecon.com/products.shtml, available Feb 5, 2002 as verified by web.archive.org).

The description and rejection of claims 1-5 and 9 are described in the 35 U.S.C § 102(b) rejection above. Claim 6 further limits claim 5 by teaching the bone marrow be cultured by seeding the cells as a density of 10^6 to 10^7 cells/cm^3 at a rotational speed of 8.5 to 25 rpm when a 5 cm diameter RWV vessel is used. Goodwin et al. teach that bone marrow cells are added to the RWV at a concentration of $1X10^6$ cells/cm^3 (Goodwin et al., col 13 lines 59-63). Schwarz et al. teach that the RWV rotates at 10 rpm (Schwarz et al., col 6, lines 35-40). While neither of the art listed above teaches

that the RWV has a 5 cm diameter vessel this would be obvious to one of ordinary skill in the art at the time the invention was made in view of Synthecon.

Synthecon teach that RWV culture systems can be made to almost any size required by the experimenter without affecting the physics of the system (Synthecon, page 2). Absent any teaching of criticality by the applicant concerning the dimensions of the RWV listed in claim 6 it would be *prima facie* obvious that one of ordinary skill in the art would recognize that the size of the RWV vessel in claim 6 is a result effective variable that depends on the size of the culture required by the experimenter, which is a matter of routine optimization (M.P.E.P. § 2144.05 II). Therefore, the invention as a whole would have been prima facie obvious at the time of filing in view of the references listed above and as such claims 1-6 and 9 are not allowable.

In the response submitted by the Applicant, the 35 U.S.C § 103 (a) rejection of claims 1-5 and 9 over Goodwin et al. and Schwarz et al. as applied to claims 1-5 and 9 above, and further in view of Yan et al. and Simpson et al. were considered but not found persuasive.

The Applicant argues that the addition of Yan et al. and Simpson et al. do not over come the deficiencies of Goodwin et al. and Schwarz et al. in teaching cartilage tissue engineered from bone marrow mesenchymal cells. As mentioned above, this argument is not commensurate with the scope of the claims for reasons previously stated above.

Therefore the rejection stands and is repeated below.

Claims 1-5, 7 and 9 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Goodwin et al. and Schwarz et al. as applied to claims 1-5 and 9 above, and further in view of Yan et al. (U. S. Patent Application Publication # 2002/0168763) and Simpson et al. (U. S. Patent Application Publication # 2002/0090725). The description and rejection of claims 1-5 and 9 are described in the 35 U.S.C § 102(b) rejection above. Claim 7 further limits the method of claim 1 by requiring TGF- β and/or dexamethasone in the culture medium.

While Goodwin et al. teach that "various growth factors" may be added to the culture medium to "emulate *in situ* conditions" (Goodwin, col 4, lines 3-5). While Goodwin et al. does not specifically teach TGF- β this would be obvious to one of ordinary skill in the art at the time the invention was made in view of Simpson et al. who teach the addition of TGF- β to the culture medium (Simpson et al., paragraph 98) to grow collagen matrices in a microgravity reactor (Simpson et al., paragraph 207) that contain cells from bone marrow (Simpson et al., paragraph 204). It would have been obvious to someone skilled in the art to modify the invention of Goodwin et al. with the teachings of Simpson et al. since both culture bone marrow cells in a microgravity reactor. The motivation comes from Goodwin et al. who desires to create a culture that emulates *in situ* conditions and one of ordinary skill in the are would recognize that TGF- β would be present in the body where bone marrow cells are cultured. The reasonable expectation of success is provided by Simpson et al. who teach the addition of TGF- β to the culture.

Likewise Goodwin et al. does not teach the addition of dexamethasone to their culture media, however this would be obvious at the time the invention was made in view of the teachings of Yan et al. Yan et al. teach the addition of dexamethasone to their culture media (Yan, paragraphs, 178 and 330) that grows bone marrow cells (Yan, paragraph 85) in a microgravity environment (Yan, paragraph 111) for bone marrow transplantation (Yan, paragraph 43) which is the same purpose as Goodwin et al. It would have been obvious to someone skilled in the art to add dexamethasone to the culture medium since Yan et al. and Goodwin et al. share the same purpose, see M.P.E.P. § 2144.06.

Therefore, the invention as a whole would have been prima facie obvious at the time of filing in view of the references listed above and as such claims 1-5, 7 and 9 are not allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

In response to this office action the applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thane Underdahl whose telephone number is (571) 272-9042. The examiner can normally be reached Monday through Thursday, 8:00 to 17:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Thane Underdahl
Art Unit 1651

Leon B. Lankford Jr
Primary Examiner
Art Unit 1651